LANGUAGE: English
SUMMARY LANGUAGE: English
AB A ***nitroreductase*** isolated and purified from Escherichia coli B has been demonstrated to have potential applications in ***ADEPT*** (antibody-directed enzyme prodrug therapy) by its ability in vitro to reduce dinitrobenzamides (e.g. 5-aziridinyl 2,4-dinitrobenzamide, CB 1954 and its bischloroethylamino analogue, SN 23862) to form cytotoxic derivatives. In contrast to CB 1954, in which either nitro group is reducible to the corresponding hydroxylamine, SN 23862 is reduced by the ***nitroreductase*** to form only the 2-hydroxylamine. This hydroxylamine can react with S-acetylthiocholine to form a species capable of producing interstrand crosslinks in naked DNA. In terms of ***ADEPT*** , SN 23862 has a potential advantage over CB 1954 in that it is not reduced by mammalian DT diaphorases. Therefore, a series of compounds related to SN 23862 has been synthesized, and evaluated as potential prodrugs both by determination of kinetic parameters and by ratio of IC50 against UV4 cells when incubated in the presence of prodrug, with and without the E. coli enzyme and cofactor (NADH). Results from the two studies were generally in good agreement in that compounds showing no increase in cytotoxicity in presence of enzyme and cofactor were not substrates for the enzyme. None of the analogues were activated by DT diaphorase isolated from Walker 256 carcinoma cells. For those compounds which were substrates for the E. coil ***nitroreductase*** , there was a positive correlation was between k(cat) and IC50 ratio. Two compounds showed advantageous properties: SN 25261 (with a dihydroxypropylcarboxamide ring substituent) which has a more than 10-fold greater aqueous solubility than SN 23862 whilst retaining similar kinetic characteristics and where a change in the position of the carboxamide group relative to the cytotoxicity ratio and k(cat) compared with SN 23862 (IC50 ratios 214 26.4 sec-1, respectively). An analogue (SN 25507) incorporating both enhanced k(cat) of 576 sec-1. This study elucidates some of the structural aids identification of further directions in the search for suitable prodrugs system.

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(FILE 'HOME' ENTERED AT 12:28:04 ON 28 APR 2004)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 12:28:37 ON 28 APR 2004
L1 50425 S METRONIDAZOLE
L2 1141824 S TARGET?
L3 583 S L1 AND L2
L4 120304 S CONJUGATE
L5 10 S L3 AND L4
L6 7 DUP REM L5 (3 DUPLICATES REMOVED)
L7 1647 S ADEPT
L8 2839 S NITROREDUCTASE
L9 82 S L7 AND L8
L10 50425 S METRONIDAZOLE
L11 2 S L9 AND L10
L12 1 DUP REM L11 (1 DUPLICATE REMOVED)